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(54) Title: ANTIPROGESTOGEN CONTAINING CONTRACEPTIVES

(57) Abstract

Disclosed are effective oral contraceptive regimens comprising an antiprogestogen phase combined with a progestogenic phase. A contraceptive regimen having: a first phase of 5-20, especially 14, sequential daily dosage units containing an anti-progestogen at a daily dosage sufficient to inhibit ovulation in the female, and a second phase of 10 to 25, especially 14, sequential daily dosage units containing a progestogen at a dosage equivalent to 40-120 µg desogestrel administered orally. To the first phase is preferentially added an estrogen such as 17β-estradiol (from 0.50 to 2.5 mg daily) to allow for the possibility of making a sequential regimen. The invention also includes a contraceptive product (i.e. the package containing the dosage unit regimen), and a process of manufacturing this product.

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ANTIPROGESTOGEN CONTAINING CONTRACEPTIVES

The invention relates generally to contraceptive preparations, and more specifically to a multiphasic preparation containing an antiprogestogen.

RU 486 ("mifepristone") has been a rather controversial drug acting as an abortifacient. Twenty-five milligrams of mifepristone administered during the follicular phase of the menstrual cycle results in inhibition of estradiol synthesis. Luukkainen et al. "Inhibition of folliculogenesis and ovulation by the antiprogesterone RU 486", Fertil.Steril., 49:961 (1988).

It has been suggested that administration of an mifepristone before the luteinizing hormone ("LH") surge of the menstrual cycle could inhibit progestogen and thus ovulation. Kekkonen et al. "Interference with ovulation by sequential treatment with the antiprogesterone RU 486 and synthetic progestin", Fertility and Sterility, 53(4): 747-750 (1990). Kekkonen et al. discloses a discontinuous regimen wherein 25 mg of mifepristone was administered daily on days 1 to 14 of the menstrual cycle followed by 3 mg of the progestogen norethisterone for days 15 to 24, followed by 5 placebo days. This regimen was administered over three cycles. Unfortunately, with this regimen, serum concentrations of follicle stimulating hormone and LH were not suppressed. Furthermore, during the administration of the progestogen, evidence of ovulation and follicle growth was found during the two first administration cycles. Such results could lead to an unwanted pregnancy or to the unnecessary exposure of a fetus to these and possibly other compounds.

A need exists for an effective contraceptive regimen which utilizes the advantages of an anti-progestogen, but is immediately effective after the first cycle of administration.

Surprisingly it has been found that by properly selecting an antiprogestogen and combining it with a progestogenic component in a contraceptive regimen administration cycle, an effective oral contraceptive regimen results, immediately effective after the first month of administration.

The invention thus includes a contraceptive regimen with: a first phase of 5-20, especially 10-20, and more especially 14, sequential daily dosage units each containing an anti-progestogen at a daily dosage sufficient to inhibit ovulation in the female, and a second phase of 10-25, especially 14, sequential daily dosage units containing a progestogen at a dosage equivalent to 40-120 µg desogestrel administered orally vis-à-vis ovulation inhibition. In the preferred embodiment (each phase containing 14 dose units), the regimen is effective even during the first month of adminstration.

To the first phase or part of the first phase is preferentially added an estrogen such as 17ß-estradiol (from 0.50 to 2.5 mg daily) to allow for the possibility of making a sequential regimen.

The daily dosage units of the contraceptive regimen are administered to a mammalian (e.g. human) female in need of, or desiring, contraception for as long as needed or desired (e.g. 14 days of first phase tablets, followed by 14 days of second phase tablets, after which the cycle is repeated if desired, etc.), and thus the invention also includes a method of contraception.

These contraceptive regimens can display several advantages including a decreased risk of inducing hematologic disorders which are currently associated with presently available oral contraceptive regimens (e.g. DVT's); a decreased chance of breast cancer since antiprogestogens are thought to prevent breast tumor development, and with a 28 day administration (e.g. with two 14 day phases) the regimen mimics a natural menstrual cycle.

The invention also includes a contraceptive product (i.e. the birth control pack containing the dosage unit regimen), and a process of manufacturing this product.

Daily dosage units (e.g. tablets and capsules) and methods for making them are well-known, see e.g. Remington's Pharmaceutical Sciences, (18th edition 1980). Known daily dosage units can be adapted to include the described ingredients.

Preferred antiprogestogens for use with the invention include 11-aryloestrane and 11-arylpregnane derivatives such as those disclosed in U.S. Patent No. 4,871,724 to Groen et al., e.g. (6ß,11ß,17ß)-11-(4-dimethylaminophenyl)-6-methyl-4',5'-dihydrospiro[estra-4,9-diene-17,2'(3'H)-furan]-3-one. Other preferred antiprogestogens for use with the invention are 11-arylsteroid compounds such as those disclosed in U.S. Patent No. 4,921,845 to de Jongh et al., e.g. (7ß,11ß,17ß)-11-(4-dimethylaminophenyl)-7-methyl-4',5'-dihydrospiro-[estra-4,9-diene-17,2'(3'H)-furan]-3-one. (11ß,17α)-17,23-epoxy-11-[4-(dimethylamino)phenyl]-19,24-dinorchola-4,9,20-trien-3-one and like compounds, in doses less than 20 mg orally per daily dosage unit may also be used. Other antiprogestogens are known. The contents of both U.S. Patent No. 4,921,845 to de Jongh et al. and U.S. Patent No. 4,871,724 to Groen et al. are incorporated by this reference for methods of making these antiprogestogens.

Doses of antiprogestogen in each daily dosage unit are sufficient to inhibit ovulation even during the first cycle of administration. Illustratively, doses will preferably be equivalent to less than 20 mg of (6ß,11ß,17ß)-11-(4-dimethylaminophenyl)-6-methyl-4',5'-dihydrospiro[estra-4,9-diene-17,2'(3'H)-furan]-3-one taken orally.

The contraceptive regimen of the invention also includes at least 10 daily dosage units containing a progestogenic component. Preferred progestogens for use

with the invention include 3-ketodesogestrel ("etonogestrel"), desogestrel, levo-norgestrel, norgestrel, norgestimate, gestodene, and other compounds with similar progestogenic activity. Desogestrel and 3-ketodesogestrel can be used in oral doses of 40 to 120 μg, especially 75 μg, per day. Equivalent doses of other progestogens can also be used. Gestodene is approximately 1.5 times as potent as these compounds. Norgestrel is about one-half as potent as levo-norgestrel. Most of these progestogens are readily commercially available.

If an estrogen is included in the first dosage units, 17β-estradiol is preferred, co-administered with the anti-progestogen at a daily dose of about 1 mg. 17β-estradiol is readily commercially available. The use of natural estrogens is preferred.

Other estrogens which can be used include ethinyl estradiol, mestranol and 17-α-ethinyl estradiol 3-methylether. As an approximation, 1 mg of 17β-estradiol is equivalent in estrogenic activity to 0.015 mg of ethinyl estradiol and 0.030 mg of mestranol.

The antiprogestogen, estrogen and progestogen ("contraceptive steroids"), or appropriate mixtures thereof are preferably incorporated into dosage units for oral administration. The term "dosage unit" generally refers to physically discrete units suitable as unitary dosages for humans or animals, each containing a predetermined quantity of active material (e.g. antiprogestogen or progestogen) calculated to produce the desired effect.

Methods and compositions for making such dosage units are well-known to those skilled in the art. For example, methods for making capsules, tablets and pills, containing active ingredients and pharmaceutical excipients, are described in the standard reference, Gennaro et al., Remington's Pharmaceutical Sciences, (18th ed., Mack Publishing Company, 1990, see especially Part 8: Pharmaceutical Preparations and Their Manufacture).

Methods of making powders, and their composition, and methods of coating pharmaceutical dosage forms are also described in Remington's (see especially chapters 88 and 90 respectively). For making dosage units, e.g. tablets, the use of conventional additives such as fillers, colorants, polymeric binders and the like is contemplated. In general any pharmaceutically acceptable additive which does not interfere with the function of the active compounds can be used.

Suitable carriers with which the compositions can be administered include lactose, starch, cellulose derivatives and the like, or mixtures thereof, used in suitable amounts. Lactose is a preferred carrier.

A process of manufacturing the combination and contraceptive kit involves mixing predetermined quantities of antiprogestogen with appropriate amounts of pharmaceutical excipients, optionally together with predetermined quantities of estrogen, and converting the mixture into first daily dosage units (e.g. by filling capsules or molding tablets with the mixture and any desired excipients); and mixing predetermined quantities of progestogen with predetermined quantities of appropriate pharmaceutical excipients and converting that mixture into second daily dosage units.

A preferred process of manufacturing the contraceptive product according to the invention involves incorporating the desired dosages of steroid (e.g. antiprogestogen with or without estrogen) into a tablet by known techniques. Tablets containing different amounts and types of steroids may be of different colors, and kept in different portions of, for example, a blister pack. The package containing the dosage units may contain 20 to 40 dosage units arranged sequentially therein. Preferably there will be 28 dosage units consisting of two phases of 14 tablets each.

A method of contraception with invention involves administering to a pre-menopausal fertile female in 20 to 40 day cycles for so long as contraception is

desired, the following: for a first 5 to 20 days, an antiprogestogen at a daily dosage sufficient to inhibit ovulation; and for the next 10 to 25 days, a progestogen at a daily dosage equivalent in progestogenic activity to 40 to 120 µg desogestrel administered orally. If contraception is still desired, the administration is continued, again starting with the first phase of tablets immediately after the first complete regimen is completed.

A preferred regimen involves administering to a female of child bearing age at the following times over a 28 day period:

(a) for 14 days an oral composition containing, in daily amounts, from 1 to 20 mg of (6ß,11ß,17ß)-11-(4-dimethylaminophenyl)-6-methyl-4',5'-dihydrospiro[estra-4,9-diene-17,2'(3'H)-furan]-3-one or equivalent amount of other antiprogestogen; and

(b) for 14 days an oral composition containing 75 µg desogestrel or equivalent amount of other progestogen.

The invention is further explained by the following illustrative EXAMPLES.

EXAMPLE I

Compositions of tablets:

A. In the first phase: (14 tablets), each containing:

Compound		Amount (mg/tablet)
(6ß,11ß,17ß)-11-(4-dimethyl-aminophenyl)-6-methyl-4',5'-dihydrospiro[estra-4,9-diene-17,2'(3'H)-furan]-3-one		20.00
17ß-estradiol		1.00
potato or corn starch		8.00
polyvinyl pyrrolidone		2.40
stearic acid		0.80
silica		0.80
dl-α-tocopherol		0.08
lactose	qsad	80.00

B. In the second phase: (14 tablets), each containing:

Compound		Amount (mg/tablet)
desogestrel		0.075
potato or corn starch		8.000
polyvinyl pyrrolidone		2.400
stearic acid		0.800
silica		0.800
dl-α-tocopherol		0.080
lactose	qsad	80.000

EXAMPLE II

A. In the first phase: (14 capsules), each containing:

Compound		Amount (mg/capsule)
(6ß,11ß,17ß)-11-(4-dimethyl-aminophenyl)-6-methyl-4',5'-dihydrospiro[estra-4,9-diene-17,2'(3'H)-furan]-3-one		20.000
potato starch		8.000
polyvinyl pyrrolidone		2.400
stearic acid		0.800
silica		0.800
dl-α-tocopherol		0.080
lactose	qsad	80.000

B. In the second phase: same as EXAMPLE I.A., but encapsulated in gelatin capsules.

EXAMPLE III

A. In the first phase: (10 tablets), each containing:

Compound		Amount (mg/capsule)
(7ß,11ß,17ß)-11-(4-dimethyl-aminophenyl)-7-methyl-4',5'-dihydrospiro[estra-4,9-diene-17,2'(3'H)-furan]-3-one		20.000
potato starch		8.000
polyvinyl pyrrolidone		2.400
stearic acid		0.800
silica		0.800
dl-α-tocopherol		0.080
lactose	qsad	80.000

B. In the second phase: same as EXAMPLE I.B., but with 20 tablets.

EXAMPLE IV

A. In the first phase: (20 tablets), each containing:

Compound		Amount (mg/capsule)
(6ß,11ß,17ß)-11-(4-dimethyl-aminophenyl)-6-methyl-4',5'-dihydrospiro[estra-4,9-diene-17,2'(3'H)-furan]-3-one		20.000
17ß-estradiol		1.500
potato starch		8.000
polyvinyl pyrrolidone		2.400
stearic acid		0.800
dl-α-tocopherol		0.080
lactose	qsad	80.000

B. In the second phase: (20 tablets), each containing:

Compound		Amount (mg/tablet)
3-ketodesogestrel		0.075
potato starch		8.000
polyvinyl pyrrolidone		2.400
stearic acid		0.800
silica		0.800
dl-α-tocopherol		0.080
lactose	qsad	80.000

EXAMPLE V

A. In the first phase:

1. A first sub-phase of 10 capsules, each containing:

Compound		Amount (mg/capsule)
(6ß,11ß,17ß)-11-(4-dimethyl-aminophenyl)-6-methyl-4',5'-dihydrospiro[estra-4,9-diene-17,2'(3'H)-furan]-3-one		20.000
corn starch		8.000
polyvinyl pyrrolidone		2.400
stearic acid		0.800
silica		0.800
dl-α-tocopherol		0.080
lactose	qsad	80.000

2. A second sub-phase of 10 capsules, each containing

Compound		Amount (mg/capsule)
(6ß,11ß,17ß)-11-(4-dimethyl-aminophenyl)-6-methyl-4',5'-dihydrospiro[estra-4,9-diene-17,2'(3'H)-furan]-3-one		20.000
17ß-estradiol		1.500
corn starch		8.000
polyvinyl pyrrolidone		2.400
stearic acid		0.800
silica		0.800
dl-α-tocopherol		0.080
lactose	qsad	80.000

C. Same as EXAMPLE I.A., but encapsulated in twenty gelatin capsules.

Claims

1. A multiphasic combination and contraceptive kit having from 20 to 40 sequential daily dosage units comprising:
a first phase of from 5 to 20 separate first daily dosage units comprising an antiprogestogen at a dosage sufficient to inhibit ovulation during administration of said first phase; and
a second phase of 10 to 25 separate second daily dosage units, each said second daily dosage unit containing a progestogen at a dosage equivalent in progestogenic activity to 40-120 µg desogestrel administered orally.

2. The multiphasic combination and contraceptive kit of claim 1 wherein said first phase daily dosage units further comprise an estrogen at a dosage equivalent in estrogenic activity to 0.50 to 2.5 mg 17ß-estradiol administered orally.

3. The multiphasic combination and contraceptive kit of claim 1 wherein said first and said second phase both consist of 14 separate daily dosage units.

4. The multiphasic combination and contraceptive kit of any one of claims 1 to 3 wherein said progestogen is selected from the group consisting of desogestrel, 3-ketodesogestrel, levo-norgestrel, gestodene, norgestimate and mixtures thereof.

5. The multiphasic combination and contraceptive kit of claim 4 wherein said progestogen is desogestrel or 3-ketodesogestrel at a quantity per dosage unit of 75 µg in said second daily dosage units.

6. The multiphasic combination and contraceptive kit of any one of claims 1 to 5 wherein said estrogen is selected from the group consisting of 17β-estradiol, ethinyl estradiol mestranol, 17-α-ethinyl estradiol 3-methylether, and mixtures thereof.

7. The multiphasic combination and contraceptive kit of claim 6 wherein said estrogen is 17β-estradiol.

8. A multiphasic contraceptive compositions comprising a plurality of sequential daily dosage units characterized in that some of said sequential daily dosage units comprise a sufficient amount of an antiprogestogen effective to inhibit ovulation during the administration thereof.

9. A process of manufacturing the combination and contraceptive kit of any one of claims 1 to 7 comprising:
mixing predetermined quantities of antiprogestogen with appropriate pharmaceutical excipients and, optionally, predetermined quantities of estrogen and converting said mixture into said first dosage units; and
mixing predetermined quantities of progestogen with predetermined quantities of appropriate pharmaceutical excipients converting said mixture into said second dosage units.

10. A method of contraception in a female comprising administering to a pre-menopausal fertile female in 20 to 40 day cycles for so long as contraception is desired, the following:

for a first 5 to 20 days, an antiprogestogen at a daily dosage sufficient to inhibit follicular growth and ovulation; and

for the next 10 to 25 days, a progestogen at a daily dosage equivalent in progestogenic activity to 40 to 120 μg desogestrel administered orally.

INTERNATIONAL SEARCH REPORT

International Application No.
[redacted]T/EP 93/02139

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K31/565

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	FERTILITY AND STERILITY vol. 53, no. 4 , April 1990 pages 747 - 750 cited in the application see the whole document ---	1-10
Y	FERTILITY AND STERILITY vol. 49, no. 6 , June 1988 pages 961 - 963 cited in the application see page 961, right column, line 6 - line 11 see page 963, left column, line 17 - line 20 see page 963, left column, line 46 - right column, line 3 --- -/--	1-10

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
28 October 1993	04. 11. 93.

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CONTRACEPT.FERTIL. SEX vol. 10, no. 6 , 1982 pages 389 - 393 see page 389 - page 392	1-10
A	TRENDS IN MEDICINAL CHEMISTRY; 9TH INT.SYMP., BERLIN, WEST GERMANY, SEPT. 14-18, 1986. IX+634P. vol. 0, no. 0 , 1987 pages 565 - 580 'Anti-Progestins - A New Approach to Contraception' see the whole document	1-10

INTERNATIONAL SEARCH REPORT

International application No.
EP 93/ 02139

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
REMARK: Although claim 10 is directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.